Gordenin talk featured at 2015 Lineberger Symposium

By Eddy Ball

NIEHS lead researcher Dmitry Gordenin, Ph.D., was one of fifteen speakers featured at the 39th annual Lineberger Symposium April 8-9 in Chapel Hill, North Carolina.

Each year organizers at the University of North Carolina School of Medicine Comprehensive Cancer Center invite leading experts in cancer research and treatment to participate in the themed symposium, highlighting exciting new developments in the field. This year's conference focused on " Personalized Medicine, the Cancer Genome Atlas, and the Future of Cancer Care *(https://unclineberger.org/symposium)* ."

Gordenin, who leads the NIEHS Mechanisms of Genome Dynamics Group, discussed his team's groundbreaking discoveries in experiments with a yeast model, during a talk titled "Pan-Cancer Analysis of APOBEC Mutagenesis." APOBEC refers to a specific family of proteins. The researchers, including Kin Chan, Ph.D., an NIEHS Intramural Research and Training Award fellow, confirmed the findings in human tumor samples, with follow-up bioinformatic analyses performed in collaboration with Les Klimczak, Ph.D. Klimczak is an NIEHS contract scientist who developed and maintains the analytical package *(http://gdac.broadinstitute.org/runs/analyses__latest/reports/cancer/BLCA/Mutation_APOBEC/nozzle.html)* that was recently integrated into The Broad Institute TCGA Genome Data Analysis Center Firehose pipeline, which performs pan-TCGA analysis on a regular basis.

Gordenin joined researchers from institutions in the U.S. and U.K., who presented findings of genomic abnormalities in a variety of cancers. (Photo courtesy of Steve McCaw)

Linked Audio

Listen to Gordenin discuss clustered mutations in this NIEHS podcast (2:16)

A newly discovered mechanism involved in cancer

Gordenin presented results of work that became a part of The Cancer Genome Atlas (TCGA) Network, indicating that APOBEC cytidine deaminases, which are enzymes that normally act in antiviral immune responses, can be a powerful source of mutations linked to cancer initiation and disease progression. Gordenin said these hypermutational patterns, or mutation clusters, stemmed from infrequent, long single-strand DNA regions.

Chan combined genetic analysis of APOBEC mutagenesis in a yeast model and in cancer genomes to further detail APOBEC mutagenic mechanisms. (Photo courtesy of Steve McCaw)

The clusters helped to identify APOBEC enzymes as a powerful source of hypermutation in several cancer types. For example, APOBEC hypermutation is observed in more than half of urinary bladder cancers, a common malignancy that causes approximately 150,000 deaths per year worldwide. The discovery of this new type of carcinogenic mutagenesis presents an exception to the traditional view that mutations occur randomly across the genome and accumulate over time.

Bladder cancer is not the only cancer in which APOBEC hypermutation is robust, Gordenin explained. The pattern is also abundant in cancers of the cervix, head, neck, breast, and lung. "It's probably in the background of many other cancers," he said. "In some of these samples [examined by the team], APOBEC mutagenesis was the dominant mutational force, producing 300 mutations per exome (300,000 per whole genome) and constituting up to 70 percent of total mutations."

Homing in on molecular targets in cancer

During the course of three major studies that combined mechanistic and bioinformatics approaches to better understand mutation processes operating in cancer, cited below, Gordenin and his collaborators identified molecular targets that may ultimately revolutionize treatment for cancers with the APOBEC mutational signature.

Greater understanding of the factors that regulate APOBEC activity may also lead to the development of cancer therapies and prevention strategies aimed at minimizing the negative effects of these proteins, while maintaining their normal functions in immunity.

Citations:

Roberts SA, Sterling J, Thompson C, Harris S, Mav D, Shah R, Klimczak LJ, Kryukov GV, Malc E, Mieczkowski PA, Resnick MA, Gordenin DA. *(http://www.ncbi.nlm.nih.gov/pubmed/22607975)* . 2012. Clustered mutations in yeast and in human cancers can arise from damaged long single-strand DNA regions. Mol Cell 46(4):424-435. (Story)

Roberts SA, Lawrence MS, Klimczak LJ, Grimm SA, Fargo D, Stojanov P, Kiezun A, Kryukov GV, Carter SL, Saksena G, Harris S, Shah RR, Resnick MA, Getz G, Gordenin DA. *(http://www.ncbi.nlm.nih.gov/pubmed/23852170)* 2013. An APOBEC cytidine deaminase mutagenesis pattern is widespread in human cancers. Nat Genet 45(9):970-976. (Story)

Cancer Genome Atlas Research Network. *(http://www.ncbi.nlm.nih.gov/pubmed/24476821)* 2014. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 507(7492):315-322. (Story)

(Eddy Ball is a contract writer for the NIEHS Office of Communications and Public Liaison)

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